

Why Are Sex and Recombination So Common?

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The abundance of sex and recombination is still one of the most puzzling questions in the theory of evolution: Most models find that recombination can evolve, but only under a limited range of parameters. Here we review the major models and supporting evidence, concentrating on recent approaches where more realistic assumptions help explain the evolution of sex and recombination under a wider parameter range: finite populations, selection over long genomes, variation in recombination across the genome, and plasticity of sex and recombination. We discuss the similarities and differences between the evolution of sex and that of recombination.

Key words: evolution of sex; sexual reproduction; recombination; epistasis; linkage disequilibrium; red queen; plasticity

Recombination and sexual reproduction are ubiquitous among higher eukaryotes. Yet their adaptive value is not fully understood. The question is particularly hard when we take into account the significant costs of sex: First, if males do not contribute any resources other than genes to the offspring, then—everything else being equal—a sexual population would produce half the number of offspring of an asexual population of the same size in any given generation and is more likely to go extinct than a sexual population. This is known as “the two-fold cost of males” (Maynard Smith 1978). Second, to reproduce, a sexual organism must find and court a mate. This goal is not always successful and usually requires time and energy while exposing the individual to predation or transmission of pathogens. Last, the mixing of genotypes exposes the sexual species to conflicts (Partridge & Hurst 1998). Conflicts can arise between males and females, where mutations that have a beneficial effect on one sex and a deleterious effect on the other can spread, resulting in increased reproduc-

tive success for the carrier but decreased success for its partner(s) and often for the entire population (Rice & Chippindale 2001a). Conflicts can also arise in a sexual population between different genes in the genome because their long-term interests are no longer identical: This includes segregation distorters (Lyttle 1991), conflicts between organelle and genome (Hurst 1993), and between the genome and parasitic DNA such as transposable elements. Altogether, the costs of sex are likely to exceed twofold often, implying that sex is maintained in the world because of a greater than twofold advantage.

The evolution of sex and recombination has been modeled at two levels: The first considers their effect on the long-term survival of the population as a whole, asking when a higher rate of sex/recombination would increase the average fitness of the population at equilibrium (Muller 1964; Crow & Kimura 1965; Lewontin 1971). The second (Nei 1967) considers the fate of an allele modifying the rate of sex or recombination, asking when a new modifier that changes their frequency would increase from rarity within the population because of the forces of natural selection.

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Recombination and Genetic Associations between Alleles^a

The classic explanation for the advantage of recombination at the level of the population is its effect on variation. When recombination results in increased variation in fitness within the population, it allows natural selection to act more effectively and would usually result in a long-term advantage. One problem with this explanation is that recombination does not always result in increased variation in fitness. This outcome can be seen through the effect of recombination on the associations between alleles, or linkage disequilibrium (LD). LD is a measure of the deviation of gametic frequencies from the expected frequencies if alleles in different loci were entirely independent of each other. LD is positive when the extreme genotypes (in terms of fitness) are more common than expected by random chance and negative when they are less common, or when the beneficial alleles are distributed too evenly in the population. Recombination breaks down associations between alleles, bringing the population closer to linkage equilibrium. This might be either advantageous or disadvantageous for

the population, depending on the sign of the initial LD.

Consider the simplest example of a two-locus, two-allele model: AB is the best genotype, ab is the worst, and Ab and aB have intermediate effects on fitness. Negative linkage equilibrium means that the intermediate genotypes (Ab and aB) are overrepresented. In such a case recombination would more often turn intermediate genotypes into extreme ones (Ab and aB to AB and ab) than the other way around, resulting in increased variation in fitness, increased opportunity for selection, and benefit for the population in the long term. If, on the other hand, linkage disequilibrium is positive to begin with, the situation is reversed: The extreme genotypes (AB and ab) are overrepresented, and recombination would more often turn them into intermediate genotypes (Ab and aB) than the other way around, resulting in decreased variation in fitness, decreased opportunity for selection, and long-term disadvantage. Altogether, recombination is expected to be advantageous for the population as a whole only if it acts on the background of negative linkage disequilibrium (Hill & Robertson 1966; Maynard Smith 1971; Felsenstein 1974; Barton 1995b; Otto & Barton 2001; Otto & Lenormand 2002). Such negative LD is likely to be a common scenario in natural populations under either negative epistasis or drift.

^aDefinitions of Terms Used in This Report.

Background selection: removal of variation genetically linked to strongly and mildly deleterious mutations; effective population size: describes the number of different chromosomes or chromosomal segments that are effectively transmitted from generation to generation as a consequence of the cumulative effects of diverse population and selective processes in finite populations; epistasis: measure of fitness interaction between alleles at different loci, in comparison with the independent (multiplicative) model. Epistasis is positive (antagonistic) when the effect of multiple deleterious mutations is less than expected by their individual effects in the multiplicative model and negative when their effect is more than expected. Similarly, epistasis is positive when additional beneficial mutations have greater effect than expected and negative when additional beneficial mutations have diminishing returns; linkage disequilibrium: measure of the associations between alleles in different loci, deviating from zero whenever certain haplotypes are more (or less) frequent than expected by random. In two loci $D = p(AB)p(ab) - p(Ab)p(aB)$; Recombination load: difference in fitness of offspring produced with recombination in comparison with ones produced without recombination; Red queen hypothesis: suggests that the coevolution of interacting species (e.g., host and parasite, predator and prey, competitors) creates an ever-changing biotic environment that can favor the evolution of sex and recombination; Selective sweep: Elimination or reduction of variation genetically linked to strongly beneficial mutations due to fast increase in frequency and ultimate fixation of these beneficial mutations (i.e., hitchhiking effect).

Epistasis and LD

One factor that can generate associations between alleles is epistatic selection. Epistasis is a measure of the fitness interaction between loci, or the deviation of the fitness function from the multiplicative model. Epistasis is positive (antagonistic) when the combined effect of multiple deleterious mutations is smaller than predicted by their individual effects in a multiplicative model and is negative (synergistic) when the situation is reversed. When only selection and mutation occur then, at equilibrium, the allelic combinations favored by epistatic

selection would be more common than expected at random. In such a case, the LD resulting from selection would at equilibrium have the same sign as the epistasis factor (Eshel & Feldman 1970; Barton 1995b). That is, when the extreme genotypes are more (less) fit on average, they would be over- (under-) represented at equilibrium. Thus, we would expect selection to favor recombination in the long term whenever epistasis, and therefore LD, is negative. In such a case recombination results in increased variation, which can be converted to increased average fitness in the population.

For comparing two populations that do not mix, a mean fitness argument is sufficient. But if we consider the evolution of increased sex or recombination in a population that is already mixing genetically at a rate higher than zero, a modifier increasing the rate of recombination under negative epistasis is not always favored in the short term. To determine the conditions allowing a modifier of recombination to evolve, we need to consider the effect of recombination on the fitness of the individuals carrying the modifier, or equivalently on the average fitness of their offspring. If the present genetic associations are a result of the current selection pressures (so the signs of disequilibrium and epistasis are the same), then recombination is more likely to be breaking down existing favorable combinations generated by selection than creating new ones: When epistasis is positive (antagonistic) extreme genotypes are more common, and the immediate effect of recombination would more often be to change extreme genotypes to intermediate ones ($AB, ab \rightarrow Ab, aB$) than the opposite. Because positive epistasis also means that the average fitness of the extreme genotypes is higher than that of the intermediates (the definition of epistasis uses geometric mean, whereas average fitness is computed using the arithmetic mean), recombination would be disadvantageous in the short term (Fig. 1). When epistasis is negative, intermediate genotypes are more common and recombination is more likely to break them down—usually also lowering the fitness

of the offspring (Fig. 1). This phenomenon is termed *recombination load* (Charlesworth & Charlesworth 1975; see Table 1). The extreme case occurs when selection is the only force acting on the population, and there are no mutations, drift, or environmental changes. Then the only modifiers of recombination that can be favored are ones that reduce the rate of recombination (Liberman & Feldman 1986; Altenberg & Feldman 1987), a result termed the *reduction principle*. Altogether, these results highlight a major problem for a recombination modifier: An individual that has survived is likely to be carrying a genetic combination that works reasonably well in the current environment. Why should such an individual take the risk, and mix its DNA to generate an unknown new combination?

There is a wide range of conditions where the long-term and the short-term effects of recombination are in conflict. Under epistatic selection and constant environment, the direct effect of a modifier elevating recombination rates on the fitness of its carriers is usually negative (unless the interaction between mutations is negative on a log scale and positive on an additive scale). However, a long-term advantage exists whenever epistasis is synergistic (Kondrashov 1988). Then the short-term disadvantage conflicts with the long-term advantage. For the overall selection on recombination to be positive in a constant environment, epistasis should be negative but weak (Feldman *et al.* 1980; Barton 1995b). A recombination modifier can also be favored in the short term, however, when the current genetic associations are not the ones favored by the present environment, as can happen if the environment has recently changed (see “Changing Environments” section).

How common is negative epistasis in natural populations? The answer remains unclear, despite many studies (see de Visser & Elena 2007 for a review). Some studies found negative epistasis (Mukai 1969; de Visser & Hoekstra 1998; Whitlock & Bourguet 2000), some found positive epistasis (Bonhoeffer *et al.* 2004; Burch

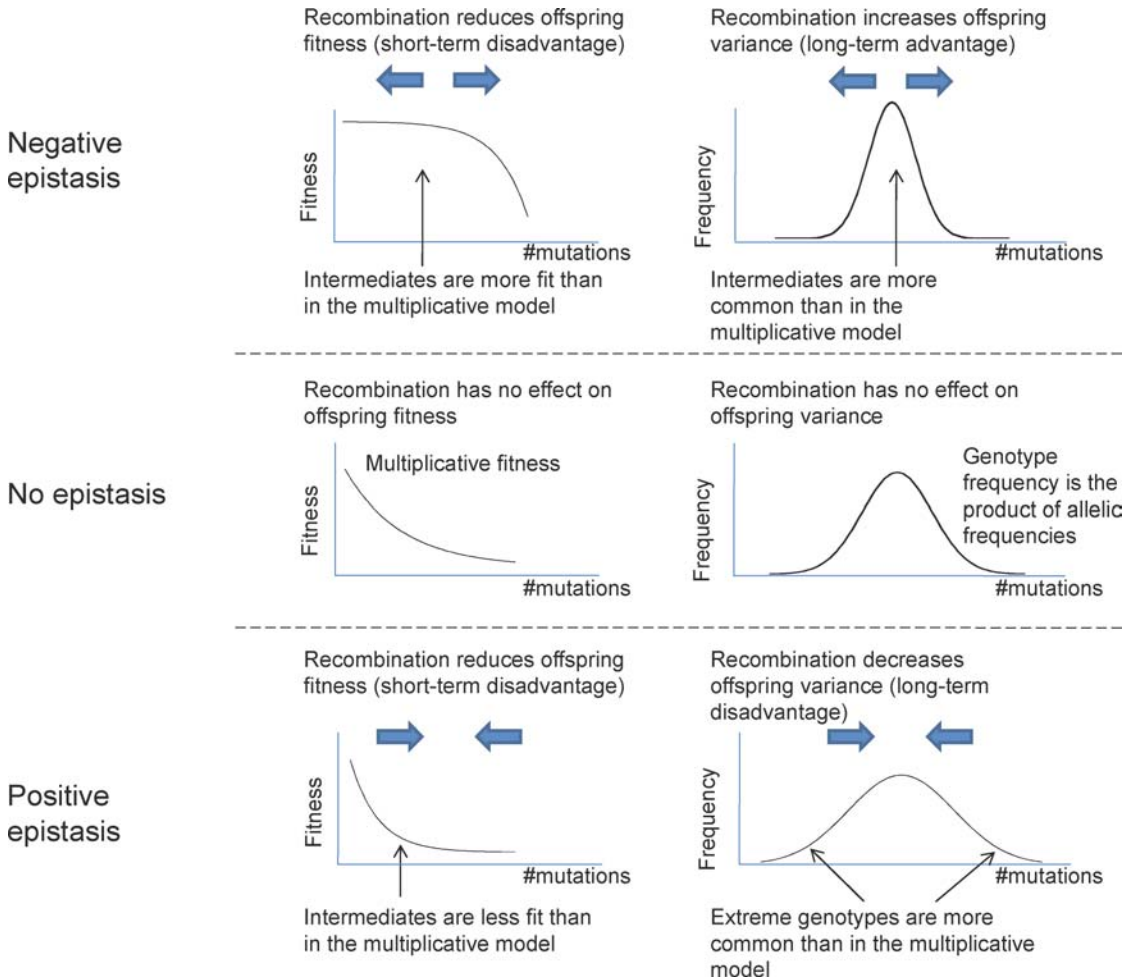


Figure 1. Epistasis, LD, and the effect of recombination. The effect of recombination on short- and long-term fitness under three epistasis regimes is illustrated. When epistasis is negative (top panels) the plot of the fitness as a function of the number of mutations is concave: The effect of multiple deleterious mutations is more than expected by their individual effects (top left panel). In such a case deleterious mutations would be distributed more uniformly at equilibrium than for multiplicative fitness (top right panel), so recombination would tend to turn intermediate genotypes into extreme ones (block arrows). This would result in both decrease in the average fitness of the offspring (short-term disadvantage) and increase in the variance of the offspring (leading to more effective selection and long-term advantage). When there is no epistasis (middle panels), fitness is multiplicative, no LD occurs, and recombination has no effect. When epistasis is positive (bottom panels) the effect of multiple mutations is less than expected by their individual effects (bottom left), and therefore the extreme genotypes are overrepresented. Recombination would thus turn extreme genotypes into intermediate ones (block arrows), resulting in both decrease in offspring average fitness (short-term disadvantage) and decrease in offspring variance (long-term disadvantage).

& Chao 2004; Zeyl 2005)—mostly in viruses, and others showed changing levels of epistasis (Elena & Lenski 1997; Kelly 2005). However, more recent studies suggest that even if synergistic epistasis is not directly detected in rela-

tively simple organisms under laboratory conditions, it might still be common among higher organisms as a result of either robustness of complex genetic networks (Bergman & Siegal 2003; de Visser, Hermisson *et al.* 2003; Wagner

2005) or competition among small groups (Peck & Waxman 2000).

Advantages of Segregation

The preceding arguments apply to recombination, but a similar case can be made for the advantages of sex due to segregation. Whereas recombination breaks down associations between alleles at different loci, bringing the population closer to linkage equilibrium, segregation breaks down associations between alleles at the same locus, bringing the population closer to Hardy–Weinberg equilibrium. Similar to recombination, segregation can increase variation in fitness within the population—but it does not have to. Segregation increases variation when the associations between alleles within loci tend to be negative (i.e., when the intermediate genotypes are overrepresented) and lowers variation in the opposite case. Fitness interactions within a locus (i.e., dominance) can result in such associations. In the common case where the homozygotes are the extreme genotypes in terms of fitness and the heterozygote has intermediate fitness, segregation would increase variation whenever the fitness of the heterozygote is higher than the average fitness of the homozygotes—or when the deleterious allele is at least partly recessive (Chasnov 2000). This is known to be the situation for many deleterious mutations. The advantage of segregation can be significantly increased if the population is not fully mixed and some inbreeding occurs. This would result in a long-term advantage for the population as a whole (Agrawal & Chasnov 2001) and, often, in selection in favor of a modifier increasing the rate of segregation (Dolgin & Otto 2003; Otto 2003).

Drift, Beneficial Mutations, and LD

The preceding models assume infinite populations. But natural populations are finite, creating other probable routes for recombination

to increase the effectiveness of selection. The consideration of a finite population size can have drastic consequences for the evolution of recombination and its possible advantages.

First, drift itself—the random sampling of genotypes in a finite population—results in associations between alleles (Muller 1964). Although the LD produced by drift is equally likely to be positive or negative, selection would not act in the same way in both cases. When LD is generated by a factor other than epistasis, selection acts to reduce it. If drift resulted in overrepresentation of extreme genotypes (positive LD), selection would be effective in eliminating the bad genotypes, rapidly bringing the population close to linkage equilibrium. If, however, drift resulted in overuniform distribution of good alleles (negative LD), the difference in fitness between the different genotypes would be small, and the approach toward linkage equilibrium would be slower. As a result of this inherent asymmetry, a finite population is expected to be found in negative LD even without epistasis (Otto & Barton 2001; Barton & Otto 2005). The combination of drift and selection can thus result in an advantage for a recombining population (see following discussion) and favor the evolution of modifiers that increase the rate of sex or recombination even without epistasis (Keightley & Otto 2006).

Another factor that can create negative associations in a finite population is beneficial mutations (Maynard Smith 1978). If, for example, a new advantageous mutation appears in just one individual, then the new allele would be 100% associated with this genotype. Again, this association can be either positive (if the new mutation occurred in a good chromosome) or negative (if it occurred in a chromosome carrying many deleterious mutations). But whereas selection is effective in removing the first type of LD through rapid increase in the frequency of the new mutation, it is less effective in breaking LD of the second type. Thus, the random occurrence of beneficial mutations would also create negative LD (Otto & Barton 1997).

The combination of common deleterious mutations and rare beneficial mutations can result in an even greater advantage for sex and recombination: In an asexual population, a beneficial mutation can arise either on a background that includes too many deleterious mutations, resulting in a genotype that is not the fittest in the population, or on a background that contains relatively few deleterious mutations, resulting in a potential for selective sweep. In the first case, the beneficial mutation is likely to be eliminated and the asexual population would suffer from a reduced rate of adaptation because of “background trapping” (Charlesworth 1994; Peck 1994; Orr 2000; Rice & Chippindale 2001b). In the second case, there is a good chance for a selective sweep that would take both the beneficial mutation and the weakly deleterious background to fixation, resulting in “evolutionary traction”: increased load of mutation in the asexual population (Manning & Thompson 1984; Hadany & Feldman 2005).

Are beneficial mutations common enough in the genome to play a significant role in the advantage of recombination? Studies (Fay *et al.* 2001; Smith & Eyre-Walker 2002; Sawyer, Kulathinal *et al.* 2003; Andolfatto 2005) suggest that the rate of advantageous substitutions in the genome is in fact high, especially when one considers both amino acid changes and mutations at noncoding regions that are likely associated with changes in gene expression.

Selection, Recombination, and Effective Population Size

As indicated in the preceding discussion, the presence of either deleterious or beneficial mutations is expected to generate negative LD in finite populations, hence justifying the long-term advantage of recombination. This long-term advantage can also be investigated in terms of reduced effectiveness of selection in finite populations when recombination is limited or absent (the so-called Hill–Robertson effect; Hill & Robertson 1966; Felsenstein 1974).

For instance, the frequent removal of deleterious mutations also removes genetically linked nucleotides, reducing the number of effective chromosomes that can pass to the next generation relative to the same population without selection. This phenomenon, known as background selection (Charlesworth *et al.* 1993; Charlesworth 1994; Hudson & Kaplan 1995), is equivalent to a reduction in the effective population size (N_e) and therefore to an increase in the magnitude of random genetic drift. An equivalent argument can be made for beneficial mutations that will also cause a relative reduction in N_e as a direct consequence of the removal of standing variation linked to advantageous mutations when they increase in frequency within a population (a “selective sweep”) (Maynard Smith & Haigh 1974; Kaplan *et al.* 1989; Gillespie 2000; Kim & Stephan 2003). Thus, in finite populations subject to selection, N_e is expected to vary with recombination (Hill & Robertson 1966; Felsenstein 1974; Birky & Walsh 1988; Charlesworth *et al.* 1993; Hilton *et al.* 1994; Kondrashov 1994; Barton 1995a; Caballero & Santiago 1995; Otto & Barton 1997; Wang *et al.* 1999); the magnitude of the relative reduction in N_e due to selection is predicted to be maximal without recombination and to decrease when recombination increases.

The concept of N_e of a species (Charlesworth & Charlesworth 1985) is an attempt to parameterize the overall effects of drift under an idealized evolutionary model (the Wright–Fisher model), including species-specific factors such as the census population size, unequal numbers of the two sexes, variance in mating success, temporal variation in population size, population subdivision, and the possible effects of selection on drift described earlier. Because the effectiveness of selection in a finite population depends on the product of the selection coefficient (s) acting on a particular mutation and N_e —not the census population size—any mechanism that reduces N_e is predicted to also reduce the effectiveness of selection (Wright

1931; Crow & Kimura 1970), allowing the random loss of potentially useful mutations present at low frequency in the species and, at the same time, increasing the probability that weakly deleterious mutations might reach high frequencies and even become fixed in the population. This reduction in effectiveness of selection because of linkage increases in magnitude with the number of sites under selection. Figure 2 illustrates the probability of fixation of beneficial mutations in a simulated genome with complete linkage as a function of the number of sites under selection.

That is, partial or total linkage is predicted to reduce the effectiveness of selection relative to an equivalent biological system with higher rates of recombination. As a consequence, modifiers that increase recombination are predicted to be beneficial to the population because that population would have a better chance to prevent the accumulation of deleterious mutations and to adapt to new environments (long-term advantage). Granted that all biological systems are finite and natural selection is always present (to various degrees), this N_e -centric view is useful in explaining the advantage of modifiers that increase recombination and ultimately the prevalence of recombination in biological systems. This perspective does not contradict the LD one presented previously but represents a complementary approach that mostly describes the evolutionary consequences. For instance, the increased drift predicted by selection can also increase negative LD (Felsenstein 1988), hence the advantages of increased recombination (see earlier discussion).

Population geneticists often find useful the study of the evolutionary consequences of recombination (or lack thereof) in terms of differences of N_e because it directly parameterizes the consequences of differences in recombination rates in terms of variation in effectiveness of selection. This N_e -centric view also has the advantage of predicting population features that can be easily measured using molecular population genetics techniques, and hence it is a testable

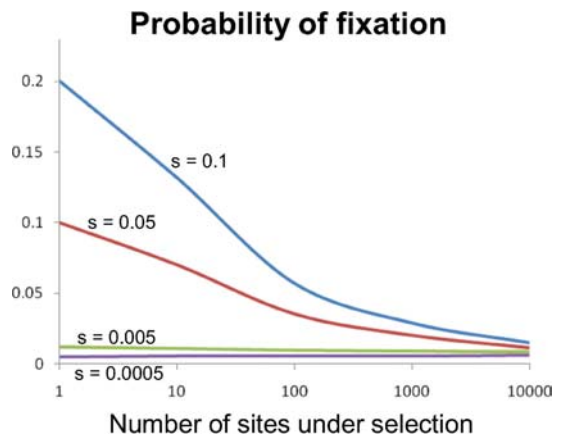


Figure 2. Effectiveness of selection in nonrecombining chromosomes. Probability of fixation of beneficial mutations as a function of a variable number of completely linked sites. Beneficial mutations with selection coefficients ($+s$) have multiplicative effects over sites and are semidominant in their effects on fitness. Results from computer simulations following a Wright–Fisher model (including mutation, selection, and drift) of a diploid population with 200 chromosomes and a mutation rate of 0.00005/site/generation. Without linkage effects, the probability of fixation observed for one site should remain constant when increasing the number of sites.

approach. For instance, the predicted variation in N_e with recombination forecasts variation in levels of neutral polymorphism, which in finite populations are expected to be positively correlated with N_e if selection occurs (see “Evidence” section).

On the other hand, the study of linkage effects in terms of a reduction in N_e allows us to study the consequences on the effectiveness of selection in quantitative terms that can be probed with genomic and evolutionary studies. For instance, under the simple case of a mutation under constant selection (s) in a diploid population and semidominance (genic selection), the probability of fixation (u) of a mutation is (Wright 1931; Kimura 1962; Moran 1961)

$$u(p) = \frac{1 - e^{-4.N_e.s.p}}{1 - e^{-4.N_e.s}}, \quad (1)$$

where N represents the actual or census population size and p represents the frequency of

the mutation in the population. It follows that when $N_e \sim N$, the probability of fixation of a new ($p = 1/2N$) mutation is

$$u = \frac{2s}{1 - e^{-4N_s}}. \quad (2)$$

For a positive s and large N , we obtain the well-known $u \approx 2s$. Equally, when N_e differs from N (e.g., due to linkage, with $N_e < N$) we obtain

$$u = 2s \frac{N_e}{N}. \quad (3)$$

That is, any reduction in N_e will be accompanied by a similar reduction in the probability of fixation for advantageous mutations. From Equation 1 we can also infer that when N_e is reduced, deleterious mutations will increase their probability of fixation exponentially.

Changing Environments

Another factor that might play a role in the evolution of recombination is environmental changes—either temporal (Charlesworth 1976; Kondrashov & Yampolsky 1996; Otto & Michalakis 1998; Waxman & Peck 1999) or spatial (Lenormand & Otto 2000). A change in the environment can have two types of effects on the evolution of recombination: First, it is likely to generate directional selection because a different genotype is now favored. Such directional selection favors the evolution of recombination when there is weak and negative epistasis in the new environment (Barton 1995b) (similar conditions to those favoring recombination at mutation–selection balance) and further favors recombination when the population is small (Burger 1999). Second, an environmental change can result in a short-term advantage for the recombining genotypes when the existing genetic associations are not the ones favored by the new environment (i.e., if the sign of epistasis has been reversed). Then recombination would break down the existing associations that have become unfavorable in the

new environment. Every such change results in a temporary advantage for recombination, but the environment (and the epistasis sign) needs to fluctuate rapidly to favor high levels of recombination (Sasaki & Iwasa 1987). Scenarios that might result in common fluctuating epistasis are based on biotic interactions: predator and prey, competition between species, and especially the coevolution of hosts and parasites.

Red Queen Hypothesis

The red queen hypothesis (Van Valen 1973) suggests that the coevolution of interacting species is a general scenario that might favor the evolution of sex and recombination. If the matching between host and parasite is genetically determined, and parasites are shorter lived than their hosts, parasites would tend to evolve to best infect the most common host genotype at any given time, thus turning this genotype into the least favorable in the next generation. Such frequency-dependent selection favors sex and recombination in various models (Hutson & Law 1981; Bell & Smith 1987; Hamilton *et al.* 1990; Howard & Lively 1994; Howard & Lively 1998; Peters & Lively 1999), but its generality is still largely controversial (Ladle *et al.* 1993; Otto & Nuismer 2004). Interestingly, red queen models seem to work best in simulations using finite populations (Howard & Lively 1994; Howard & Lively 1998). In finite populations, the coevolution of hosts and parasites can result in a combination of factors that might favor the evolution of sex in addition to fluctuating epistasis: strong selection, beneficial mutations, and a significant increase in drift as different genotypes go through bottlenecks, severely reducing N_e . The synergistic interaction of the different factors (e.g., drift, selection, and mutation) can result in a further increased advantage for sex and recombination and calls for pluralistic models (West *et al.* 1999; Cooper *et al.* 2005; Bruvo *et al.* 2007).

Variation in Recombination Across Genomes

Classically, arguments for the advantage of sexual reproduction and recombination have focused on comparing species with and without meiotic recombination. Quantitative examination of recombination and its effects on the efficacy of selection reveals that genomes of species with sexual reproduction can represent a heterogeneous environment because recombination rates often vary by several orders of magnitude across the genomes in almost all recombining organisms.

For years, the genomic units of variation in N_e and of effectiveness of selection across genomes because of interaction between selection and linkage were either whole chromosomes or large genomic regions, with the underlying assumption being that only regions with severely limited recombination would exhibit reduced effectiveness of selection. In regions of severely limited recombination, the decrease in effectiveness of selection would involve (and even out) many genes. However, more recent population genetic studies suggest that, most likely, no species has genomic regions with recombination rates high enough to eliminate the effects of selection in decreasing the effectiveness at close sites. Estimates of N_e and effectiveness of selection indicate, and simulations using realistic parameters also suggest, that in regions with high recombination rates each gene or even each exon might represent a unit for the effectiveness of selection (Comeron *et al.* 1999; Comeron & Kreitman 2002; Comeron & Guthrie 2005). That is, the study of recombination and selection in finite populations in terms of N_e alters its classic meaning, where N_e is influenced by many species factors expected to act on the whole genome, to predict that N_e would thus also vary among and across chromosomes, with local intrachromosomal variation in regions with high recombination (Comeron & Kreitman 2002).

Variation in N_e both within and across chromosomes predicts that the effectiveness of selection might vary among genes depending on its precise genomic location and has intriguing consequences on genome organization and the dynamics of gene movement across genomes. Also, the advantages of modifiers of recombination are expected to vary across genomes in species with sexual reproduction, implying that many local modifiers might be favored over the commonly assumed scenario of one modifier with broad effects. This possibility is also supported by models for the advantage of recombination that suggest that modifiers tightly linked to beneficial mutations (i.e., local) would be favored over long-range modifiers with loose linkage with any selected mutation (Otto & Barton 1997; Otto 2003).

Plasticity of Sex and Recombination

All the foregoing models implicitly assume that the rate of recombination (or the probability of sexual reproduction) is equal for all the individuals that carry the same allele at the modifier locus. However, both recombination and sex in fact vary significantly according to the individual's condition: Recombination increases in response to environmental changes (Hoffman & Parsons 1991; Korol *et al.* 1994), including starvation (Davis & Smith 2001), heat and cold (Zhuchenko *et al.* 1986; Grell 1978), parasite infection (Gemmell *et al.* 1997; West *et al.* 2001), and behavioral competition (Belyaev & Borodin 1982). Furthermore, the tendency to reproduce sexually varies among facultative sexuals in response to stresses (Bell 1982; Grishkan *et al.* 2003), including starvation (Kassir *et al.* 1988; Abdullah & Borts 2001), DNA damage, and even competition (Van Kleunen & Fischer 2003). Could this variation within the population help explain the evolution and maintenance of sex and recombination?

Recent works have considered the effect of a modifier that increases recombination (in haploids) or sex (in either haploids or diploids) when the individual's condition is poor. In contrast with the results obtained for a uniform modifier, such a fitness-associated modifier can evolve even in an infinite population, when starting from linkage equilibrium (Gessler & Xu 2000; Hadany & Beker 2003), and even when the cost of sex is high (Hadany & Otto 2007). This finding can be understood by considering the "abandon ship" advantage of such modifiers: They tend to break away from unfit genetic backgrounds by recombination or segregation and link to the better genetic backgrounds (Fig. 3). An association thus appears between the modifier allele for fitness-associated recombination/sex and beneficial alleles at other loci. As a result, the modifier has a short-term advantage even if it has no long-term advantage at all (e.g., in the extreme case of one fitness locus). This allows the evolution of some level of sexual reproduction or recombination over almost all the parameter range.

Also, fitness-associated recombination or sex often results in an advantage in terms of average population fitness because it tends to break down beneficial combinations at a lower rate than it creates them. In terms of LD, whereas uniform recombination can only bring the population closer to linkage equilibrium, fitness-associated recombination can in fact generate positive LD between fitness loci, suggesting a long-term advantage for recombination even without negative LD.

In diploid populations, sex and recombination are not identical in their effect. Whereas condition-dependent sex evolves under a wide parameter range (Hadany & Otto 2007), fitness-associated recombination evolves under much more restricted conditions and requires maternal effects (Agrawal *et al.* 2005). This is because a modifier of recombination in a diploid organism cannot affect its own probability of moving to a different genetic background (just its probability of moving to the other chromosome) and because stress at the

level of the organism does not supply much information regarding which chromosome is better.

Evidence for the Advantage of Sex and Recombination

Recombination rates are genetically controlled, with double-strand breaks playing a critical role in initiating recombination in many species (Lichten & Goldman 1995; Romanienko & Camerini-Otero 1999; Baudat *et al.* 2000; McKim *et al.* 2002; Caryl *et al.* 2003). There is substantial variation in recombination between species (Awadalla 2003), even between closely related species. For instance, there is almost a twofold difference between two *Drosophila* species (*D. melanogaster* and *D. mauritiana*) that diverged only 2.5 million years ago (True *et al.* 1996), and humans and chimps show differences in both large- and small-scale recombination rates (Ptak *et al.* 2005). More importantly, there are also considerable differences in recombination rates among individuals of the same species (Lawrence 1958; Green 1959; Simchen & Stamberg 1969; Brooks & Marks 1986; Broman *et al.* 1998; Jeffreys *et al.* 2001; Yu *et al.* 2001). Genetically controlled variation within species therefore defines the possibility of selection on recombination rates and its modifiers.

Recombination Increases the Efficacy of Selection

As discussed, several models of selection and recombination forecast that genetic linkage in natural populations is equivalent to a reduction in effectiveness of selection (the Hill–Robertson effect), and several lines of evidence support this prediction. Analyses of the rates of protein evolution show a reduction of the effectiveness of selection in genomic regions where recombination is severely reduced or absent (Takano 1998; Comeron & Kreitman 2000; Bachtrog & Charlesworth 2002; Betancourt & Presgraves

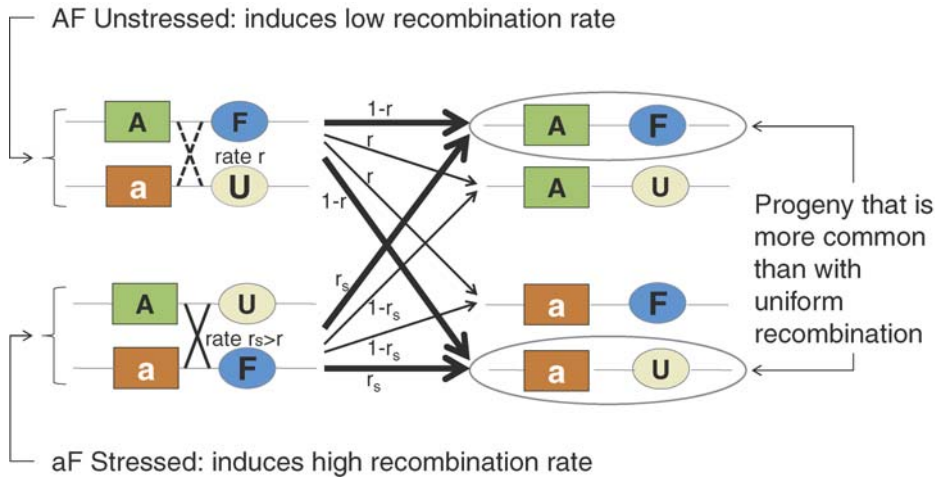


Figure 3. The advantage of fitness-associated recombination in a two-locus haploid model. The rate of combination is determined by averaging the recombination tendencies of the two haploids, where the allele U codes for uniform recombination at the same rate at all times, while the allele F codes for fitness-associate recombination—a higher rate of recombination when fitness is low. When the allele F is linked to the fitter fitness allele (A), recombination between AF and aU occurs at a low rate, r . When the allele F is linked to the deleterious allele (a), recombination between aF and AU occurs at a higher rate, r_s . As a result, an association is generated between the allele F and the better fitness allele, A, leading to the spread of fitness-associated recombination in the population.

2002; Bustamante *et al.* 2002; Marais *et al.* 2004; Haddrill *et al.* 2007). An extreme case of variation within genomes is the Y chromosome, which in many species can be assumed to be largely nonrecombining DNA transmitted only through males. Molecular evolution and genomic analyses reveal that the efficacy of selection is reduced in the Y chromosome, accumulating more deleterious mutations and taking advantage of a lower fraction of beneficial mutations than most other chromosomal regions of the same genome (Bachtrog 2003; Gerrard & Filatov 2005). In this regard, the study of recent nonrecombining chromosomes (e.g., neo-Y chromosomes) is highly informative. Evolutionary studies of the neo-Y chromosome in *Drosophila miranda* show an excess of deleterious mutations, including many frameshift or nonsense mutations, an accumulation of transposable elements (Steinmann & Steinmann 1997; Steinmann & Steinmann 2001; Bachtrog & Charlesworth 2002; Bachtrog 2004), and inactivation of gene expression (Bachtrog 2006)—all signs of its rapid

degeneration. Studies of synonymous codon usage bias, a trait likely under weak selection in many eukaryotes and therefore expected to react to subtle differences in N_e , also show reduced adaptation to optimal codon usage in regions with strongly reduced recombination (Kliman & Hey 1993; Comeron *et al.* 1999; Zurovcova & Eanes 1999; Comeron & Kreitman 2002; Machado *et al.* 2002; Marais & Piganeau 2002; Kliman & Hey 2003; Marais *et al.* 2003; Haddrill *et al.* 2007). A possible caveat associated with studies that compare the Y chromosome to other genomic regions is that in many vertebrate species the Y chromosome appears to be subject to a higher mutation rate (Haldane 1935; Makova & Li 2002; Ellegren & Fridolfsson 2003; Sandstedt & Tucker 2005). This difference in mutation rates does not immediately explain a difference in the ratio of deleterious to beneficial mutations observed when one compares Y chromosomes to autosomal regions, but it certainly makes a direct comparison more complex.

Recombination Allows Higher Levels of Polymorphism and Increased Rates of Adaptation

The approach of investigating the evolutionary consequences of variation in recombination rates in terms of variation in N_e can be easily tested experimentally by means of measuring neutral polymorphism. In finite populations, polymorphism at the DNA level is expected to be proportional to the product of N_e and the mutation rate. Indeed, genomic regions with reduced rates of crossing over, and likely overall recombination, show reduced levels of neutral polymorphism relative to regions of the same genomes with higher rates—a trend that has been documented in many different eukaryotic genomes (Miller *et al.* 1975; Berry *et al.* 1991; Aguade *et al.* 1994; Aquadro *et al.* 1994; Stephan 1994; Moriyama & Powell 1996; Nachman 1997; Kraft *et al.* 1998; Nachman 1998; Stephan & Langley 1998; Zurovcova & Eanes 1999; Bachtrog & Charlesworth 2000; Przeworski *et al.* 2000; Andolfatto & Przeworski 2001; Baudry *et al.* 2001; Cutter & Payseur 2003). These results strongly support the concept that the evolutionary consequences of recombination can be investigated in terms of variation in N_e and that reduced recombination reduces N_e . Also, the observed reduction in polymorphism levels in the Y chromosome of most species would make the prediction of N_e reduced because of linkage effects conservative if this chromosome has higher mutation rates (see earlier).

Modifiers of Recombination with Local Effects

Recent population genetic and genomic studies in *Drosophila* indicate that N_e and the efficacy of selection vary not only along chromosomes with large-scale changes in recombination but also between adjacent genes and along genes that are located in equivalent large-scale recombination environments (Comeron *et al.* 1999; Comeron & Kreitman 2000; Com-

eron & Kreitman 2002; Comeron & Guthrie 2005). These results favor the hypothesis of local variation in effectiveness of selection owing to the interaction between selection and linkage across recombining genomes. Importantly, such a scenario would favor modifiers of recombination with local, possibly even gene-specific, effects. This possibility of local modifiers of recombination is in agreement with models and simulations that predict that modifiers tightly linked to beneficial mutations would have a higher probability of increasing in frequency within a population than that of more loosely linked modifiers (see earlier). Local modifiers increasing recombination between sites under selection might be “hot spots” of recombination (i.e., sequences with a high recombination rate per physical unit) but may also be neutral sequences that increase recombination and the effectiveness of selection at adjacent sequences simply by increasing the distance between them. Under this scenario, intronic sequences could be viewed as local modifiers of recombination with gene-specific effects. This new hypothesis therefore incorporates the dynamics of genome evolution into explanations of the evolution and advantage of recombination (Comeron & Kreitman 2000; Comeron 2001; Comeron & Kreitman 2002; Comeron 2005). A direct prediction of this model is the positive relationship between measures of effectiveness of selection and intronic presence, a trend that is observed in *Drosophila* (Comeron & Kreitman 2002).

Experimental Evolution

Another approach to the study of the advantages of sex compares the evolution of sexual and asexual populations in artificial selection experiments. The results are mixed: In some studies sex tends to result in an advantage in a constant environment, but not in adaptation (Zeyl & Bell 1997), whereas in others sexuals tended to have an immediate disadvantage but to adapt more successfully in the end (Carson 1958; McPhee & Robertson 1970; Rice 1994;

Greig *et al.* 1998; Lynch 1998; Fridolfsson & Ellegren 2000; Rice & Chippindale 2001b; Colegrave *et al.* 2002; Goddard *et al.* 2005), especially in large populations (Colegrave 2002).

Limits to the Advantage of Recombination?

Because recombination is a variable trait within species, recombination rate can itself be a trait susceptible to natural selection. In agreement with this prediction, artificial selection experiments to increase recombination rates are successful in most species (Chinnici 1971; Kidwell 1972). Moreover, most artificial selection experiments in traits other than recombination rates also end up with increased recombination as a parallel outcome (Sismanidis 1942; Flexon & Rodell 1982; Charlesworth & Charlesworth 1985; Zhuchenko *et al.* 1985; Burt & Bell 1987; Gorodetskii *et al.* 1990; Korol & Iliadi 1994; Rodell *et al.* 2004). These observations strongly indicate that recombination rates can increase but are naturally constrained below their possible maximum even though higher rates per se would increase the effectiveness of selection (all else being equal) and hence be selected for under many circumstances. The observation that the limits that linkage impinges on the effectiveness of selection are almost never eliminated also points to the potential costs of recombination that would add to certain costs of sex, such as possible mutagenic effects and recombination load. In short, there is increasing support for the concept that recombination rates are not only variable and controlled by selection but also represent species-specific equilibria that characterize the short- and long-term advantages of recombination as well as its costs.

Sex versus Recombination

In most of this report we considered the similar aspects of sex and recombination—both allow the mixing of different genotypes. However, sex and recombination are different in many re-

spects. First, sexual reproduction generates two types of genetic mixing—recombination and segregation. Second, most of the costs associated with sexual reproduction do not apply to recombination in itself. This makes the abundance of obligatory sexuals particularly puzzling: We could think, for example, of the evolution of a modifier that reduces the frequency of sex by half while doubling the rate of recombination. Such a modifier would result in costs reduced by up to half while maintaining the same average rate of recombination. One possible solution to that puzzle is that facultative sex might be unstable, tending to evolve into obligate asexuality and then to go extinct. This might favor the evolution of constraints that would make facultative sex less likely (Nunney 1989; Burt 2000). However, the question becomes even harder when we consider that facultatively sexual organisms can switch to sexual reproduction when their condition is poor and reproduce asexually otherwise (as many of them indeed do; Bell 1982), resulting in an even greater disadvantage for obligate sex (Hadany & Otto 2007). Putting the question in its extreme form: Why should a fit female choose to reproduce sexually in a species with no paternal care? She is unlikely to gain genetic benefits from mixing her own genotype and would still pay the “twofold cost of males” by producing male offspring. It therefore seems that other aspects of sexual reproduction must be involved in the evolution of obligatory sex. One likely candidate is sexual selection, which offers a direct advantage to fit individuals—more offspring for males, and more grand-offspring (and later-generation progeny) for females, through the reproductive advantage of their sons. Under strong sexual selection, obligatory sex can indeed have an adaptive advantage over facultative sex, even when the cost of sex is significant (Hadany & Beker 2007).

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Conflicts of Interest

The authors declare no conflicts of interest.

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